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EXAMINER

REES, D

ART UNIT

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DATE MAILED:

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This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

10-23/95

5/18/95

3/23/95

3/24/95

This action is made final.

This application has been examined  Responsive to communication filed on 3/24/95  
A shortened statutory period for response to this action is set to expire 3 month(s). 0 days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- Notice of References Cited by Examiner, PTO-892.
- Notice of Art Cited by Applicant, PTO-1449.
- Information on How to Effect Drawing Changes, PTO-1474.
- Notice of Draftsman's Patent Drawing Review, PTO-948.
- Notice of Informal Patent Application, PTO-152.
- \_\_\_\_\_

Part II SUMMARY OF ACTION

- Claims 1, 3 - 20, 45 - 59 are pending in the application.  
Of the above, claims \_\_\_\_\_ are withdrawn from consideration.
- Claims \_\_\_\_\_ have been cancelled.
- Claims \_\_\_\_\_ are allowed.
- Claims 1, 3 - 20, 45 - 59 are rejected.
- Claims \_\_\_\_\_ are objected to.
- Claims \_\_\_\_\_ are subject to restriction or election requirement.
- This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
- Formal drawings are required in response to this Office action.
- The corrected or substitute drawings have been received on \_\_\_\_\_ Under 37 C.F.R. 1.84 these drawings are  acceptable;  not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
- The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_ has (have) been  approved by the examiner;  disapproved by the examiner (see explanation).
- The proposed drawing correction, filed \_\_\_\_\_, has been  approved;  disapproved (see explanation).
- Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has  been received  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.
- Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
- Other

**Part III DETAILED ACTION**

***Claim Rejections - 35 USC § 112***

1. Claims 1,3-20, 45-59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a) Claim 1 is indefinite in reciting "probe intensities being associated with a nucleic acid probe on a chip" in that it is not clear how the probe intensity is "associated" with the probe. For example, it is not clear whether an "intensity" value is an intrinsic property of each individual probe or if the "intensity" is actually a reflection of the extent of hybridization of probe molecules at a specific site on the chip. The claim might be amended to clarify this point.

b) Claim 1 is further indefinite in reciting "substantially proportional" in that it is not clear how "substantially" is defined.

c) Claim 1 is further indefinite in reciting "said associated probe" in that it is the probe intensities which are said to "associated" with a nucleic acid probe; therefore this term lacks proper antecedent basis.

d) Claim 1 is further indefinite in reciting "calling said unknown base" in that it is unclear how "calling" is defined; i.e. there appears to be a step missing. The comparing step provides a value with reference to standards? a blank? and the calling step is based on this value? Some recitation should be made in the claims of this intermediate step(s) as it appears to be an essential link between "comparing" and "calling".

e) Claim 4 is indefinite in reciting "calling said unknown base as being a base" in that it is unclear what the unknown base is specifically being "called". The claim might be amended to recite --calling said unknown base an A, T, C or G-- or alternatively --identifying an unknown base--. Further "said probe" lacks proper antecedent basis. It is additionally unclear what "a predetermined ratio value is" in that it is unclear what the reference point for this value is.

f) Claim 6 is indefinite in reciting the "step of sorting" said plurality of probe intensities in that it is not clear what the probe intensities are sorted into (i.e how does this differ from a comparison or the calling step?).

g) Claim 9 is indefinite in reciting "a wild type probe intensity" in that it is not clear how "wild-type" is defined in comparison with the "reference sequence" . Further the recitation of "each probe intensity of a probe" because it is unclear how a single probe can have more than one intensity (as implied by the use of the term "each").

h) Claims 9 and 10 are further indefinite in reciting "first ratios" and "second ratios" in that these ratios are not clearly defined with respect to probes and probe intensities. The problem seems to be mainly one of antecedent basis -it is not clear how "a probe" is to be distinguished from "each probe" in claim 10.

i) Claim 12 is indefinite in reciting "comparing said ratio of neighboring nucleic acid probes" in that it is not clear if the ratios of neighboring nucleic acid probes are compared to each other or to the reference sequence or both.

j) Claim 13 and 14 are indefinite in reciting "Probe intensities of a probe" in that it is not clear how "a" probe generates more than one intensity. It is further how probe intensities are "compared" to statistics and further what the outcome of this step is.

k) Claim 16 is indefinite in reciting "related probe intensities" in that it is not clear how the probes are related.

l) Claim 17 is indefinite in reciting "subtracting a background intensity" in that it is not clear how a background intensity is determined (before hybridization of the probes?).

m) Claim 45 is indefinite in reciting "the step of calling the unknown base". See paragraph 1d.

n) Claim 47 is indefinite in reciting "substantially proportional". See paragraph 1b.

o) Claim 49 is indefinite in reciting "calling step" and "predetermined ratio value". See paragraph 1d and 1e.

p) Claim 51 is indefinite in reciting "substantially proportional" (see paragraph 1b). The claim is further indefinite in reciting "to said associated nucleic acid probe hybridizing with a reference nucleic acid sequence" in that an associated nucleic acid probe hybridizing with a reference sequence has not been previously recited. Similarly the recitation of "said associated nucleic acid probe hybridizing with said sample sequence" lacks proper antecedent basis in this claim. Claim 51 is further indefinite in reciting "calling said unknown base according to results of said comparing step" (paragraph 1d).

q) Claim 52 is indefinite in reciting "calculating first ratios of a wild type probe intensity associated with a wild type probe" , in that it is not clear how a " wild-type probe is defined" (how is it distinguished from the reference sequence?). It is further unclear how "a probe" is distinguished from "each probe".

r) Claim 54 is indefinite in reciting "calling said unknown base". See paragraph 1d.

s) Claim 56 is further indefinite in reciting "comparing the ratio of neighboring nucleic acid probes" in that it is not clear what is being compared: the intensity ratios? And if the latter - of neighboring probes to each other? to reference probes?

t) Claim 57 is unclear in reciting "said plurality of probe intensities being associated with a nucleic acid probe in that it is unclear how a "plurality" of intensities are associate "a"

nucleic acid probe". The claim is further unclear in reciting "comparing at least one of said probe intensities with said statistics"-in that it is not clear exactly what is being compared or what the outcome of this comparison is that allows one to "call" an unknown base sequence.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order

for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1,3-20, 45-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor et al. WO 92/10588 25 June 1992, in view of Weiss et al (USPAT 5470710, filed Oct 22, 1993) and Stockham et al. (USPAT 5273632, Dec 28, 1993).

Fodor et al. WO 92/10588 25 June 1992, teaches an SBH method wherein initial data resulting from a detection system is an array of data indicative of fluorescent intensity versus location of a substrate. Spurious data points are removed in the method to determine an average of data points. In general the data are fitted to a base curve and statistical measures are used to remove spurious data (page 17, lines 26-40). The detection method provides a positional localization of the region where hybridization takes place and upon having collected all the data indicating the subsequences present in the target sequence, this data may be aligned by overlap to reconstruct the entire sequence of the target (pages 35-36). Fodor also teaches that pixel density may be evaluated over a region to determine the locations and actual extent of a positive signal (this may be interpreted as performing a comparison of intensities in order to "call" a site) (page 76). Fodor teaches that although the method is most directly applicable to sequencing, the invention is also

applicable to fingerprinting, mapping and general screening of specific interactions. Thus the method of Fodor clearly suggests the comparison of hybridization of wild type sequences to mutant sequences or to reference sequences. The method of Fodor et al. differs from that of the present invention in that intensity ratios are not compared as a means on determining the identity of a base, rather it is the location of the signal which is called (although as noted above; distinguishing between different ratios of signal intensities is a part of the method of Fodor which allows one to determine a positive signal at any one site).

Weiss et al (USPAT 5470710, filed Oct 22, 1993) teaches a system which converts the signals obtained from a pattern of multiplex reaction products hybridized with fluorescent probes into a string of nucleotides corresponding to the nucleotide sequence (see abstract). The data acquired is interpreted by an algorithm that yields a "called sequence". Weiss teaches that a CCD snapshot of hybridization signals may be obtained and pixel values may be determined and averaged (column 14, lines 55-63). Ratios of signal intensities are determined using this system and statistics used to calculate standard deviations of sample intensities vs background signals. (see example 7). Further, Stockham et al. (USPAT 5273632, Dec 28, 1993) teaches a method of computerized analysis of the visual images of DNA sequence ladders. A digital lane signal is converted by Fourier transformation to a frequency spectrum. When all the lane signals

from a set of four lanes have been deconvolved using the same lifter function, the signals are normalized to each other (column 4, lines 56-70). A deconvolved signal is subjected to a preliminary peak detection step. A group of putative peaks is established by selecting all peaks which exceed a pre-established threshold intensity. The putative peaks include all peaks whose height (intensity) exceeds the value of the threshold function at their position, i.e a comparison of the ratios of intensities at a segment of a lane is used to determine an average peak height. Determination of threshold values is performed for each of the four lanes and a procedure for registering each of the four lanes is used which preferably places the peaks not only in the correct spatial order, but minimizes the variance of spacing. Preferably the alignment procedure uses high speed sorting across the lanes using a four lane interdependent adjustment of peak positions (columns 9-10). The nucleotide sequence is the correspondence between peak order among the different lanes and the lane associated with each peak, a step referred to as base calling. The methods of Weiss and Stockham do not set any limits on the numbers of ratios that can be determined using their computer system. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time that the invention was made to use the computer algorithms of Stockham and Weiss to interpret the data inputted from the SBH system of Fodor, given that one could "call" a site

based on the intensity of a signal produced by an associated probe at that site and thus assign an identity to that site. It would be further well within the skill of the ordinary artisan, given the conventionality of standards or reference sequences to determine a predetermined ratio of signal intensities in order to assess whether a positive or negative signal is obtained at that site.

(It therefore appears that the issue of patentability in the present application resides in distinguishing over the "comparing" and "calling" processes of the computer algorithms of Weiss and Stockham and reciting this clearly in the claims).

3. The following references are additionally cited as relevant to programs designed to distinguish between ratios of intensities of light:

Rutenberg et al. (USPAT 4965725, Oct 23, 1993) teaches the use of a neural net system which is a commercially available statistical classifier which identifies a location of interest (in this example a cell) by measurement of integrated optical densities which are the sum of pixel grey values for the object corrected for optical errors. Based on data obtained from a

primary classifier, a secondary classifier is used to check specific areas of the specimen that are deemed to require further screening or classification. Such further examination may be effected by reliance on the already obtained digitized image data for the selected areas of a specimen or by taking additional data components (columns 3, lines 56-60, column 4, lines 7-18) Information within the system is stored in the strength of connections known as weights. In an asynchronous fashion, each processing element computes the sum of products of the weight of each input line multiplied by the signal level (usually 0 or 1) on that input line . If the sum of products exceeds a preset activation threshold, the output processing element is set to 1, if less, it is set to zero. Rutenberg also teaches that "a threelayer neural network can always find a representation that will map any input pattern to any desired output pattern".

Bacus (USPAT 4741043, April 26, 1988) teaches the use of a neural net system to determine the staining of DNA in cytological specimens. The system is calibrated for the optical density of an object , and incoming data may be converted to lookup tables in an imaging processing board so that the output shown optical density can be linearly added to proportionally reflect directly, in this instance the amounts of DNA (column 7, lines 4-11).

4. No claims are allowed.

5. Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7939. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees  
Dianne Rees

Dec 14, 1995

*W. Gary Jones*  
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12/14/95